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SEARCH REQUEST FORM

7-133

Examiner # (Mandatory): L. E. Crane Requester's Full Name: same

Art Unit 1623 Location (Bldg/Room#): 8D-14 Phone (circle 305 306 308) 4639

Serial Number: 09/288,344 Results Format Preferred (circle): PAPER DISK E-MAIL

Title of Invention See attached copy of claims

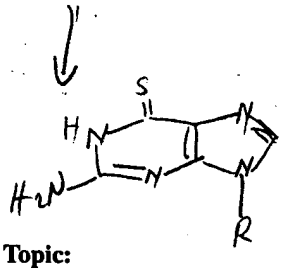
Inventors (please provide full names): "

Earliest Priority Date: 09/24/98

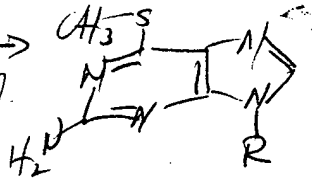
Keywords (include any known synonyms registry numbers, explanation of initialisms):

Please see claim 22 for key word disease conditions

Please search the keyword diseases with the following chemical formulas;. NOTE: Crohn's disease seemes to be antoher term which might be helpful in this search.



and → R is H, open



Search Topic:

Please write detailed statement of the search topic, and the concept of the invention. Describe as specifically as possible the subject matter to be searched. Define any terms that may have a special meaning. Give examples of relevant citations, authors, etc., if known. You may include a copy of the abstract and the broadcast or most relevant claim(s).

Point of Contact:
Mary Hale
Technical Info. Specialist
CM1 12D16 Tel: 308-4258

241
20
7
20
298

1652
1639-49

25hrs

STAFF USE ONLY

Searcher: Mary

Searcher Phone #:

Searcher Location:

Date Picked Up: 7/19/99

Date Completed:

Clerical Prep Time:

Terminal Time: 13

Number of Databases: 1

Type of Search

- N.A. Sequence
- A.A. Sequence
- Structure (#)
- Bibliographic
- Litigation1
- Fulltext
- Procurement
- Other

Vendors (include cost where applicable)

- STN ✓
- Questel/Orbit
- Lexis/Nexis
- WWW/Internet
- In-house sequence systems (list)
- Dialog
- Dr. Link
- Westlaw
- Other (specify)

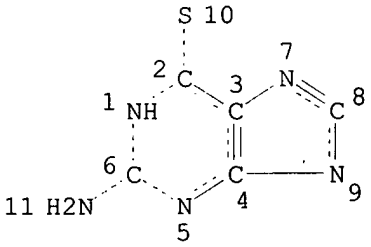
PTO-1590 (2-99)

Crane
288344

=> str

=> d l5 que stat;d l6 que stat;fil medl,hcaplus,biosis,embase;s l5 and l6

L1 STR



NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

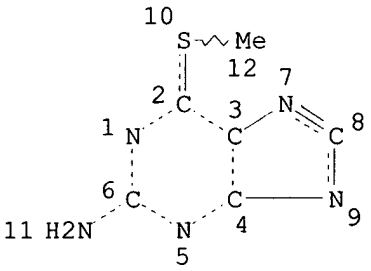
GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 11

STEREO ATTRIBUTES: NONE
L5 214 SEA FILE=REGISTRY SSS FUL L1

100.0% PROCESSED 514 ITERATIONS 214 ANSWERS
SEARCH TIME: 00.00.01

Mercapto pur
6-thio pur

L3 STR



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DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 12

STEREO ATTRIBUTES: NONE
L6 59 SEA FILE=REGISTRY SSS FUL L3

100.0% PROCESSED 579 ITERATIONS 59 ANSWERS
SEARCH TIME: 00.00.01

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COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                       241.20     540.42

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)              SINCE FILE      TOTAL
                                                           ENTRY    SESSION
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L7             0 FILE MEDLINE
L8            43 FILE HCAPLUS
L9             0 FILE BIOSIS
L10            0 FILE EMBASE

TOTAL FOR ALL FILES
L11           43 L5 AND L6

=> s l11 and (gastrointestin? disorder or inflam? bowel disease or crohn)

L12            0 FILE MEDLINE
L13            0 FILE HCAPLUS
L14            0 FILE BIOSIS
L15            0 FILE EMBASE

TOTAL FOR ALL FILES
L16            0 L11 AND (GASTROINTESTIN? DISORDER OR INFLAM? BOWEL DISEASE OR
                 CROHN)

=> fil reg;e "6-mercaptopurine"/cn 5

COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                        20.51     560.93

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                                                           ENTRY    SESSION
CA SUBSCRIBER PRICE                                         0.00     -18.36

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STRUCTURE FILE UPDATES:   17 JUL  99  HIGHEST RN 228123-53-3
DICTIONARY FILE UPDATES:  18 JUL  99  HIGHEST RN 228123-53-3

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 13, 1999
```

Please note that search-term pricing does apply when
conducting SmartSELECT searches.

```
E1            1      6-MERCAPTOOCTANOIC ACID/CN
E2            1      6-MERCAPTOPURIN/CN
E3            1 --> 6-MERCAPTOPURINE/CN
E4            1      6-MERCAPTOPURINE 2'-DEOXYRIBONUCLEOSIDE/CN
E5            1      6-MERCAPTOPURINE 2'-DEOXYRIBOSIDE/CN

=> s e3;e "6-thioguanine"/cn 5

L17           1 6-MERCAPTOPURINE/CN


E1            1      6-THIOCYANATORIBOFLAVIN/CN
E2            1      6-THIOCYANOCARVACROL/CN
E3            1 --> 6-THIOGUANINE/CN
E4            1      6-THIOGUANINE PICRATE MONOHYDRATE/CN
E5            1      6-THIOGUANINE RIBONUCLEOSIDE/CN

=> s e3

L18           1 6-THIOGUANINE/CN

=> fil medl,hcaplus,biosis,embase,wpids

COST IN U.S. DOLLARS                              SINCE FILE      TOTAL
                                                     ENTRY    SESSION
FULL ESTIMATED COST                                   7.70     568.63

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)        SINCE FILE      TOTAL
                                                     ENTRY    SESSION
CA SUBSCRIBER PRICE                                   0.00     -18.36

FILE 'MEDLINE' ENTERED AT 16:45:22 ON 19 JUL 1999

FILE 'HCAPLUS' ENTERED AT 16:45:22 ON 19 JUL 1999
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=> s (l17 or mercaptopurine) and (l18 or thioguanine)

L19         406 FILE MEDLINE
L20         478 FILE HCAPLUS
L21         453 FILE BIOSIS
L22        1549 FILE EMBASE
'CN' IS NOT A VALID FIELD CODE
L23          22 FILE WPIDS

TOTAL FOR ALL FILES
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L24 2908 (L17 OR MERCAPTOPURINE) AND (L18 OR THIOGUANINE)

=> s l24 and (gastrointestin? inflam? bowel disease or ibd or crohn?)

L25 5 FILE MEDLINE
L26 3 FILE HCAPLUS
L27 4 FILE BIOSIS
L28 5 FILE EMBASE
L29 1 FILE WPIDS

TOTAL FOR ALL FILES
L30 18 L24 AND (GASTROINTESTIN? INFLAM? BOWEL DISEASE OR IBD OR CROHN?)

=> dup rem l30

PROCESSING COMPLETED FOR L30
L31 10 DUP REM L30 (8 DUPLICATES REMOVED)

=> d tot all

L31 ANSWER 1 OF 10 HCAPLUS COPYRIGHT 1999 ACS DUPLICATE 1
AN 1998:202674 HCAPLUS
DN 128:266250
TI Use of i.v. azathioprine or 6-**mercaptopurine** to treat **Crohn**'s disease
IN Sandborn, William J.
PA Glaxo Wellcome Inc., USA
SO U.S., 11 pp.
CODEN: USXXAM
DT Patent
LA English
IC ICM A61K031-52
ICS A61K031-415
NCL 514262000
CC 1-7 (Pharmacology)
Section cross-reference(s): 63
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	US 5733915	A	19980331	US 95-413783	19950330

AB A therapeutic method for the treatment of **Crohn**'s disease is provided, comprising administering to a patient in need of said treatment an i.v. dose of azathioprine or 6-**mercaptopurine**, or a pharmaceutically acceptable deriv. thereof. Patients receiving high doses of azathioprine administered via continuous i.v. infusion, showed a rapid increase in the levels of 6-**thioguanine** nucleotide in RBCs, concomitant with a rapid improvement in these patients clin. picture.
ST intravenous infusion azathioprine **mercaptopurine Crohn** disease
IT Corticosteroids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(corticosteroid-intolerant **Crohn**'s disease; i.v. infusion of azathioprine or 6-**mercaptopurine** for **Crohn**'s disease treatment)
IT Diseases (animal)
(fistula, **Crohn**'s fistulous disease; i.v. infusion of azathioprine or 6-**mercaptopurine** for **Crohn**'s

disease treatment)
IT **Crohn**'s disease
Immunosuppressants
(i.v. infusion of azathioprine or 6-**mercaptopurine** for **Crohn**'s disease treatment)
IT Infusions (drug delivery systems)
(i.v.; i.v. infusion of azathioprine or 6-**mercaptopurine** for **Crohn**'s disease treatment)
IT Steroids, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(steroid-dependent **Crohn**'s disease; i.v. infusion of azathioprine or 6-**mercaptopurine** for **Crohn**'s disease treatment)
IT 53-03-2, Prednisone
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(i.v. infusion of azathioprine or 6-**mercaptopurine** for **Crohn**'s disease treatment)
IT **50-44-2**, 6-**Mercaptopurine**
RL: BAC (Biological activity or effector, except adverse); MFM (Metabolic formation); THU (Therapeutic use); BIOL (Biological study); FORM (Formation, nonpreparative); USES (Uses)
(i.v. infusion of azathioprine or 6-**mercaptopurine** for **Crohn**'s disease treatment)
IT 446-86-6, Azathioprine
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(i.v. infusion of azathioprine or 6-**mercaptopurine** for **Crohn**'s disease treatment)
IT 50-66-8, 6-Methylmercaptopurine **154-42-7D**, 6-**Thioguanine**, nucleotides
RL: BOC (Biological occurrence); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); OCCU (Occurrence)
(i.v. infusion of azathioprine or 6-**mercaptopurine** for **Crohn**'s disease treatment)

L31 ANSWER 2 OF 10 HCAPLUS COPYRIGHT 1999 ACS DUPLICATE 2
AN 1998:189955 HCAPLUS
DN 128:252417
TI Azathioprine: state of the art in inflammatory bowel disease
AU Sandborn, W. J.
CS Mayo Clinic, Rochester, MN, USA
SO Scand. J. Gastroenterol., Suppl. (1998), 33(225), 92-99
CODEN: SJGSB8; ISSN: 0085-5928
PB Scandinavian University Press
DT Journal; General Review
LA English
CC 1-0 (Pharmacology)
AB A review with 37 refs. The use of 6-**mercaptopurine** (6MP) and its prodrug azathioprine (AZA) for inflammatory bowel disease (**IBD**) has increased in recent years. The pharmacol., patient response in controlled trials, new formulations and routes of administration and safety for these agents are reviewed. AZA is rapidly converted to 6MP, which is then further metabolized to the active metabolites, the 6-**thioguanine** nucleotides (6TGN). The half-life of 6TGN in erythrocytes is prolonged and weeks to months may be required to reach steady state. This prolonged time to 6TGN steady state may help explain the clin. observation that prolonged treatment (3-4 mo) with 6MP/AZA for

IBD is required before a therapeutic response occurs. Controlled trials of 6MP (1.5 mg/kg/d) or AZA (1.0-3.0 mg/kg/d) support the following treatment indications for 6MP/AZA: inflammatory **Crohn**'s disease; fistulizing **Crohn**'s disease; steroid-sparing; and remission maintenance. Controlled trials of AZA (1.5-2.5 mg/kg/d) in UC have suggested efficacy for the indications of steroid sparing and remission maintenance, as well as a possible effect in chronically active disease. A therapeutic response appears to require .gtoreq. 17 wk for most patients, and it has been suggested that a greater cumulative dose of AZA may result in increased likelihood of response to AZA. A recent pilot study suggested that administration of an IV loading dose of AZA (20-44 mg/kg over 36 h) may decrease the time to response in **Crohn**'s disease patients treated with AZA, perhaps by administering a portion of the necessary cumulative dose more rapidly. Two recent pharmacokinetic studies demonstrated that use of a delayed release oral AZA formulation which delivers AZA directly to the ileocolon markedly reduces systemic absorption of AZA. This "topical" or "local" approach to AZA treatment of **IBD** holds the promise of equal or improved efficacy with a significant redn. in toxicity, and dose-ranging clin. trials with delayed release oral AZA are planned in the near future. Side effects of AZA/6MP include pancreatitis, fever, nausea, leukopenia, infection, and hepatitis.

It appears that the risk of malignancy during or following monotherapy with AZA/6MP for **IBD** is not increased relative to the general population. AZA/6MP therapy is efficacious and reasonably safe for selected patients with **IBD**. Indications for treatment with AZA/6MP include refractory **Crohn**'s disease, fistulizing **Crohn**'s disease, steroid-dependent **Crohn**'s disease, **Crohn**'s disease remission maintenance, and possibly refractory UC, steroid dependent UC, and UC remission maintenance. The use of these immune modifier drugs in patients with **IBD** represents a significant therapeutic advance.

ST azathioprine inflammation bowel disease therapy review

IT Inflammatory bowel diseases
(azathioprine in treatment of inflammatory bowel disease in humans)

IT 446-86-6, Azathioprine
RL: ADV (Adverse effect, including toxicity); BPR (Biological process); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(azathioprine in treatment of inflammatory bowel disease in humans)

L31 ANSWER 3 OF 10 MEDLINE
AN 1998175511 MEDLINE
DN 98175511
TI Azathioprine: state of the art in inflammatory bowel disease.
AU Sandborn W J
CS Mayo Clinic, Rochester, MN, USA.
SO SCANDINAVIAN JOURNAL OF GASTROENTEROLOGY. SUPPLEMENT, (1998) 225 92-9.
Ref: 37
Journal code: UCT. ISSN: 0085-5928.
CY Norway
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 199807
EW 19980703
AB INTRODUCTION: The use of 6-**mercaptopurine** (6MP) and its prodrug

azathioprine (AZA) for inflammatory bowel disease (**IBD**) has increased in recent years. The pharmacology, patient response in controlled trials, new formulations and routes of administration and safety for these agents are reviewed. PHARMACOLOGY: AZA is rapidly converted to 6MP, which is then further metabolized to the active metabolites, the 6-**thioguanine** nucleotides (6TGN). The half-life of 6TGN in erythrocytes is prolonged and weeks to months may be required to reach steady state. This prolonged time to 6TGN steady state may help explain the clinical observation that prolonged treatment (3-4 months) with 6MP/AZA for **IBD** is required before a therapeutic response occurs. CLINICAL RESPONSE: Controlled trials of 6MP (1.5 mg/kg/d) or AZA (1.0-3.0 mg/kg/d) support the following treatment indications for 6MP/AZA: inflammatory **Crohn**'s disease; fistulizing **Crohn**'s disease; steroid-sparing; and remission maintenance. Controlled trials of AZA (1.5-2.5 mg/kg/d) in UC have suggested efficacy for the indications of steroid sparing and remission maintenance, as well as a possible effect in chronically active disease. A therapeutic response appears to require > or = 17 weeks for most patients, and it has been suggested that a greater cumulative dose of AZA may result in increased likelihood of response to AZA. A recent pilot study suggested that administration of an i.v. loading dose of AZA (20-44 mg/kg over 36 h) may decrease the time to response in **Crohn**'s disease patients treated with AZA, perhaps by administering a portion of the necessary cumulative dose more rapidly. Two recent pharmacokinetic studies demonstrated that use of a delayed release oral AZA formulation which delivers AZA directly to the ileocolon markedly reduces systemic absorption of AZA. This 'topical' or 'local' approach to AZA treatment of **IBD** holds the promise of equal or improved efficacy with a significant reduction in toxicity, and dose-ranging clinical trials with delayed release oral AZA are planned in the near future. SAFETY: Side effects of AZA/6MP include pancreatitis, fever, nausea, leukopenia, infection, and hepatitis. It appears that the risk of malignancy during or following monotherapy with AZA/6MP for **IBD** is not increased relative to the general population. CONCLUSIONS: AZA/6MP therapy is efficacious and reasonably safe for selected patients with **IBD**. Indications for treatment with AZA/6MP include refractory **Crohn**'s disease, fistulizing **Crohn**'s disease, steroid-dependent **Crohn**'s disease, **Crohn**'s disease remission maintenance, and possibly refractory UC, steroid dependent UC, and UC remission maintenance. The use of these immune modifier drugs in patients with **IBD** represents a significant therapeutic advance.

CT Check Tags: Human
Azathioprine: AD, administration & dosage
Azathioprine: AE, adverse effects
Azathioprine: PK, pharmacokinetics
*Azathioprine: TU, therapeutic use
Half-Life
Immunosuppressive Agents: AD, administration & dosage
Immunosuppressive Agents: AE, adverse effects
Immunosuppressive Agents: PK, pharmacokinetics
*Immunosuppressive Agents: TU, therapeutic use
Inflammatory Bowel Diseases: BL, blood
*Inflammatory Bowel Diseases: DT, drug therapy
Odds Ratio
Randomized Controlled Trials

6-Mercaptopurine: TU, therapeutic use
RN 446-86-6 (Azathioprine); **50-44-2 (6-Mercaptopurine)**
CN 0 (Immunosuppressive Agents)

L31 ANSWER 4 OF 10 MEDLINE
AN 97390640 MEDLINE
DN 97390640
TI 6-MP metabolite levels: a potential guide to **Crohn**'s disease therapy.
AU Sandborn W J
SO GASTROENTEROLOGY, (1997 Aug) 113 (2) 690-2.
Journal code: FH3. ISSN: 0016-5085.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199710
EW 19971005
CT Check Tags: Human
Antimetabolites: ME, metabolism
Antimetabolites: TU, therapeutic use
*Antimetabolites, Antineoplastic: ME, metabolism
*Antimetabolites, Antineoplastic: TU, therapeutic use
Azathioprine: TU, therapeutic use
Chromatography, High Pressure Liquid
Crohn Disease: BL, blood
***Crohn Disease: DT, drug therapy**
Crohn Disease: ME, metabolism
Methylthioinosine: BL, blood
Methylthioinosine: ME, metabolism
Thioguanine: BL, blood
Thioguanine: ME, metabolism
***6-Mercaptopurine: ME, metabolism**
***6-Mercaptopurine: TU, therapeutic use**
RN **154-42-7 (Thioguanine)**; 342-69-8 (Methylthioinosine); 446-86-6 (Azathioprine); **50-44-2 (6-Mercaptopurine)**
CN 0 (Antimetabolites); 0 (Antimetabolites, Antineoplastic)

L31 ANSWER 5 OF 10 MEDLINE DUPLICATE 3
AN 97038429 MEDLINE
DN 97038429
TI Quantitation of 6-**thioguanine** in peripheral blood leukocyte DNA in **Crohn**'s disease patients on maintenance 6-**mercaptopurine** therapy.
AU Cuffari C; Seidman E G; Latour S; Theoret Y
CS Department of Pediatrics, Hopital Sainte-Justine, Universite de Montreal, QC, Canada.
SO CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, (1996 May) 74 (5) 580-5.
Journal code: CJM. ISSN: 0008-4212.
CY Canada
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199704
EW 19970401
AB The effects of 6-**mercaptopurine** (6MP) in inflammatory bowel disease are believed to be primarily mediated by its metabolite 6-**thioguanine** (6TG). Our aim was to develop an assay for measuring leukocyte DNA 6TG levels in patients with **Crohn**'s disease, and to correlate them with levels of 6TG in erythrocytes. Heparinized blood was obtained from 15 adolescent **Crohn**'s disease patients

receiving 6MP at an average dose of 1.3 mg.kg-1 day-1 (range 0.8-1.6 mg.kg-1 day-1) for a mean of 23.7 months (range 3-71 months). Leukocyte DNA and erythrocyte 6TG levels were measured by an HPLC assay. Leukocyte 6TG levels ranged from 100 to 2305 pmol/mg DNA, while erythrocyte 6TG levels ranged from 64 to 1038 pmol/8 x 10(8) red blood cells, demonstrating significant interpatient variability. Leukocyte DNA 6TG levels correlated directly with erythrocyte 6TG levels, as measured by the Spearman rank correlation coefficient ($p < 0.05$). The HPLC measurement of erythrocyte and leukocyte DNA 6TG levels can be useful clinically in monitoring compliance, as well as perhaps to tailor drug metabolite levels to achieve the desired clinical effect.

CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adolescence
Adult
*Antimetabolites, Antineoplastic: BL, blood
Child
Chromatography, High Pressure Liquid: MT, methods
***Crohn Disease: BL, blood**
Crohn Disease: DT, drug therapy
DNA: BL, blood
*DNA: CH, chemistry
Erythrocytes: CH, chemistry
*Immunosuppressive Agents: ME, metabolism
*Leukocytes: CH, chemistry
Leukocytes: ME, metabolism
Linear Models
Patient Compliance
***Thioguanine: BL, blood**
***6-Mercaptopurine: ME, metabolism**

RN **154-42-7 (Thioguanine); 50-44-2 (6-Mercaptopurine);** 9007-49-2 (DNA)

CN 0 (Antimetabolites, Antineoplastic); 0 (Immunosuppressive Agents)

L31 ANSWER 6 OF 10 MEDLINE DUPLICATE 4

AN 97106897 MEDLINE

DN 97106897

TI 6-**Mercaptopurine** metabolism in **Crohn**'s disease: correlation with efficacy and toxicity.

AU Cuffari C; Theoret Y; Latour S; Seidman G

CS ~~Department of Pediatrics, Univ~~ersite de Montreal, Canada.

SO GUT, (1996 Sep) 39 (3) 401-6.
Journal code: FVT. ISSN: 0017-5749.

CY ENGLAND: United Kingdom

DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 199703

EW 19970302

AB BACKGROUND: 6-**Mercaptopurine** (6-MP) has confirmed short and longterm efficacy in the treatment of **IBD**. However, the relation between its metabolism, efficacy, and side effects is not well understood.
AIMS: To assay 6-MP metabolites and to correlate levels with drug compliance, disease activity, and adverse effects of treatment. PATIENTS: Heparinised blood was obtained prior to daily administration of 6-MP in 25 adolescent **Crohn**'s disease patients (14 ileocolitis, 11 colitis) receiving 1.2 (range 0.4-1.6) mg/kg/day for a mean of 17 (range 4-65)

months. METHODS: Erythrocyte free bases 6-**thioguanine** (6-TG) and 6-methyl-**mercaptopurine** (6-MMP) were measured (pmol/8 x 10(8) red blood cells) using reverse phase high performance liquid chromatography. RESULTS: Disease activity (modified Harvey-Bradshaw index) improved significantly with 6-MP ($p = 0.001$). Clinical remission was achieved in 72% of patients, who stopped taking prednisone, or were successfully weaned to a low alternate day dose (< 0.4 mg/kg/OD). Remission correlated well with erythrocyte 6-TG ($p < 0.05$), but not 6-MMP levels. Neutropenia was associated with 6-MP use ($p < 0.005$), but did not correlate with erythrocyte 6-MP metabolite levels. One patient refractory to 6-MP had 6-TG, but no measureable 6-MMP production, suggesting deficient thiopurine methyl-transferase activity or poor compliance. 6-MP induced complications (hepatitis, pancreatitis, and marrow suppression) were generally associated with increased 6-MMP levels. CONCLUSIONS: These results suggest that high performance liquid chromatography measurement of erythrocyte 6-MP metabolites may provide a quantitative assessment of patient responsiveness and compliance to treatment. The data support an immunosuppressive role for 6-TG, and potential cytotoxicity of raised 6-MMP levels.

CT Check Tags: Human; Support, Non-U.S. Gov't
Adolescence
Adult
Child
Chromatography, High Pressure Liquid
Crohn Disease: BL, blood
***Crohn Disease: DT, drug therapy**
Erythrocytes: ME, metabolism
*Immunosuppressive Agents: ME, metabolism
*Immunosuppressive Agents: TU, therapeutic use
Patient Compliance
Thioguanine: BL, blood
Treatment Outcome
6-Mercaptopurine: AE, adverse effects
***6-Mercaptopurine: ME, metabolism**
***6-Mercaptopurine: TU, therapeutic use**

RN **154-42-7 (Thioguanine); 50-44-2 (6-Mercaptopurine)**
CN 0 (Immunosuppressive Agents)

L31 ANSWER 7 OF 10 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1995:280768 BIOSIS
DN PREV199598295068
TI 6-**Mercaptopurine** (6-MP) metabolite measurement in **IBD** patients' neutrophils correlates with drug efficacy.
AU Cuffari, C. (1); Seidman, E. (1); Theoret, Y.
CS (1) Div. Gastroenterol., Dep. Pediatr., Cent. Recherche, Hop. Ste-Justine, Univ. Montreal, Montreal Canada
SO Gastroenterology, (1995) Vol. 108, No. 4 SUPPL., pp. A803.
Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association and Digestive Disease Week San Diego, California, USA May 14-17, 1995
ISSN: 0016-5085.
DT Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Cytology and Cytochemistry - Human *02508
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508

Pathology, General and Miscellaneous - Therapy *12512
Digestive System - Pathology *14006
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - Digestive System *22014
Pharmacology - Immunological Processes and Allergy *22018
Toxicology - Pharmacological Toxicology *22504
Pediatrics *25000

BC Hominidae *86215

IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Gastroenterology (Human Medicine, Medical Sciences); Hematology (Human Medicine, Medical Sciences); Pathology; Pediatrics (Human Medicine, Medical Sciences); Pharmacology; Toxicology

IT Chemicals & Biochemicals
6-**MERCAPTOPURINE**; 6-**THIOGUANINE**

IT Miscellaneous Descriptors
ADOLESCENT; ERYTHROCYTE; GASTROINTESTINAL AGENT; IMMUNOSUPPRESSANT-DRUG; INFLAMMATORY BOWEL DISEASE; LEUKOCYTE; LEUKOPENIA; MEETING ABSTRACT; 6-**MERCAPTOPURINE**; 6-**THIOGUANINE**

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN **50-44-2** (6-**MERCAPTOPURINE**)
154-42-7 (6-**THIOGUANINE**)

L31 ANSWER 8 OF 10 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.

AN 92307418 EMBASE

DN 1992307418

TI The clinical pharmacology of 6-**mercaptopurine**.

AU Lennard L.

CS Univ. Dept. Medicine/Pharmacology, Section Pharmacology/Therapeutics, Royal Hallamshire Hospital, Glossop Road,Sheffield S10 2JP, United Kingdom

SO European Journal of Clinical Pharmacology, (1992) 43/4 (329-339).
ISSN: 0031-6970 CODEN: EJCPAS

CY Germany

DT Journal; General Review

FS 016 Cancer
022 Human Genetics
025 Hematology
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
030 PharmacologyPharmacology

LA English

CT Medical Descriptors:
***crohn disease: DT, drug therapy**
*graft rejection: DT, drug therapy
*graft rejection: PC, prevention
*kidney transplantation
*leukemia: DT, drug therapy
*metabolic activation
clinical article
controlled study

drug blood level
drug efficacy
drug metabolism
enzyme activity
erythrocyte
female
gastrointestinal disease: SI, side effect
genetic polymorphism
human
intestine
intravenous drug administration
leukopenia: SI, side effect
liver
major clinical study
male
neutropenia: SI, side effect
oral drug administration
priority journal
rash: SI, side effect
review
Drug Descriptors:
***6 thioguanine nucleotide: CR, drug concentration**
***6 thioguanine nucleotide: AN, drug analysis**
***6 thioguanine nucleotide: PK, pharmacokinetics**
*azathioprine: DO, drug dose
*azathioprine: AE, adverse drug reaction
*azathioprine: PK, pharmacokinetics
*azathioprine: CR, drug concentration
*azathioprine: DT, drug therapy
*drug metabolite: PK, pharmacokinetics
*drug metabolite: AN, drug analysis
*drug metabolite: CR, drug concentration
***mercaptopurine: PK, pharmacokinetics**
***mercaptopurine: DO, drug dose**
***mercaptopurine: CB, drug combination**
***mercaptopurine: IT, drug interaction**
***mercaptopurine: CR, drug concentration**
***mercaptopurine: DT, drug therapy**
***mercaptopurine: AE, adverse drug reaction**
*tioguanine: DT, drug therapy
*tioguanine: CR, drug concentration
*tioguanine: PK, pharmacokinetics
*tioguanine: AE, adverse drug reaction
allopurinol: CB, drug combination
allopurinol: IT, drug interaction
hypoxanthine phosphoribosyltransferase: EC, endogenous compound
methotrexate: IT, drug interaction
methotrexate: DT, drug therapy
methotrexate: CB, drug combination
thiopurine methyltransferase: EC, endogenous compound
xanthine oxidase: EC, endogenous compound
unclassified drug
RN (azathioprine) 446-86-6; (**mercaptopurine**) 31441-78-8, **50-44-2**, 6112-76-1; (tioguanine) **154-42-7**; (allopurinol) 315-30-0; (hypoxanthine phosphoribosyltransferase) 9016-12-0; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (thiopurine methyltransferase) 67339-09-7; (xanthine oxidase) 9002-17-9

L31 ANSWER 9 OF 10 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 77155265 EMBASE
DN 1977155265

TI Clinical use of immunosuppressive drugs. II.
AU Gerber N.L.; Steinberg A.D.
CS Arthr. Rheum. Branch, Nat. Inst. Arthr. Metab. Dig. Dis., NIH, Bethesda, Md. 20014, United States
SO Current Therapeutics, (1976) 17/6 (109-124).
CODEN: CUTHDB
DT Journal
FS 037 Drug Literature Index
026 Immunology, Serology and Transplantation
030 Pharmacology
LA English
AB In controlled trials in patients with rheumatoid arthritis, high dose cyclophosphamide and azathioprine have been shown to be clearly beneficial when compared with placebo. In uncontrolled studies in dermatological diseases, azathioprine, 6 **mercaptopurine**, hydroxyurea, methotrexate, and azaribine have proven effective in treating psoriasis. Similarly, azathioprine, cyclophosphamide and methotrexate have all been used with success in treating pemphigus and pemphigoid, although none is effective in controlling acute pemphigus. In controlled studies in patients with psoriasis and psoriatic arthritis, azathioprine and methotrexate have been shown to be better than placebo. In hematological diseases, insufficient data has been accumulated to evaluate the efficacy of immunosuppressive drug treatment in patients with erythroid aplasia or sideroblastic anemia. Cyclophosphamide may be efficacious in inhibiting circulating anticoagulants in patients who need continued replacement of clotting factors. Azathioprine, 6 **mercaptopurine**, cyclophosphamide and vincristine have been used successfully in treating patients with idiopathic thrombocytopenic purpura, and some patients with auto immune hemolytic anemia may benefit from the addition of purine analogues. However, the use of immunosuppressive therapy seems to accelerate the presence of hematological malignancies in patients with macroglobulinemia. In gastro intestinal diseases, uncontrolled studies have shown nitrogen mustard, 6 **mercaptopurine** and azathiprine to be of modest benefit to patients with ulcerative colitis and **Crohn**'s disease. In a controlled trial azathioprine plus prednisone proved more effective than prednisone alone in sustaining remission in patients with **Crohn**'s disease. In patient's with either chronic active hepatitis or primary biliary cirrhosis, however, there seems to be no benefit from immunosuppressive therapy for primary treatment of these diseases.
CT Medical Descriptors:
*blood disease
*clinical study
***crohn disease**
*drug comparison
*immunosuppressive treatment
*enteropathy
*pemphigoid
*pemphigus vulgaris
*drug therapy
*psoriasis
*rheumatoid arthritis
*thrombocytopenia
*ulcerative colitis
major clinical study
therapy
Drug Descriptors:
*tioguanine
*azaribine
*azathioprine

*chlorambucil
*chlormethine
*cyclophosphamide
*hydroxyurea
*immunosuppressive agent
***mercaptopurine**
*methotrexate
*placebo
*prednisone
*vinblastine

RN (tioguanine) **154-42-7**; (azaribine) 2169-64-4; (azathioprine) 446-86-6; (chlorambucil) 305-03-3; (chlormethine) 51-75-2, 55-86-7, 82905-71-3; (cyclophosphamide) 50-18-0; (hydroxyurea) 127-07-1; (**mercaptopurine**) 31441-78-8, **50-44-2**, 6112-76-1; (methotrexate) 15475-56-6, 59-05-2, 7413-34-5; (prednisone) 53-03-2; (vinblastine) 865-21-4

L31 ANSWER 10 OF 10 MEDLINE
AN 73202804 MEDLINE
DN 73202804
TI Cytotoxic drugs in treatment of nonmalignant diseases.
AU Anonymous
SO ANNALS OF INTERNAL MEDICINE, (1972 Apr) 76 (4) 619-42. Ref: 288
Journal code: 5A6. ISSN: 0003-4819.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 197310
CT Check Tags: Animal; Human
Anti-Inflammatory Agents: PD, pharmacology
Antineoplastic Agents: PD, pharmacology
*Antineoplastic Agents: TU, therapeutic use
Arthritis, Rheumatoid: DT, drug therapy
Azathioprine: TU, therapeutic use
Chlorambucil: TU, therapeutic use
Colitis, Ulcerative: DT, drug therapy
Crohn Disease: DT, drug therapy
Cyclophosphamide: TU, therapeutic use
Hepatitis: DT, drug therapy
Immune Complex Diseases: DT, drug therapy
Immunosuppressive Agents: PD, pharmacology
Infection: DT, drug therapy
Liver Cirrhosis, Biliary: DT, drug therapy
Lupus Erythematosus, Systemic: DT, drug therapy
Methotrexate: TU, therapeutic use
Nephrotic Syndrome: DT, drug therapy
Ophthalmia, Sympathetic: DT, drug therapy
Psoriasis: DT, drug therapy
Thioguanine
Uveitis: DT, drug therapy
Wegener's Granulomatosis: DT, drug therapy
6-Mercaptopurine: TU, therapeutic use

=> s (l5 or l6 or l17 or l18 or mercaptopurine or thioguanine) and (gastrointest? or inflam? bowel? or ibd or crohn or colitis or lymphocytic)

L32 1327 FILE MEDLINE
L33 118 FILE HCAPLUS
L34 440 FILE BIOSIS

L35 2082 FILE EMBASE
COMBINATION OF STRUCTURE AND TEXT TERMS NOT VALID
The query entered contains both search terms created by structure-building or screen commands and text search terms. L#s created via the STRUCTURE or SCREEN commands must be searched in the structures files separately from text terms or profiles. The L# answer sets from structure searches can be used in crossover searches and can be combined with text terms.

=> s (l5 or l6) and (gastrointest? or inflam? bowel? or ibd or crohn? or colitis)

L36 2 FILE MEDLINE
L37 2 FILE HCAPLUS
L38 0 FILE BIOSIS
L39 3 FILE EMBASE
COMBINATION OF STRUCTURE AND TEXT TERMS NOT VALID
The query entered contains both search terms created by structure-building or screen commands and text search terms. L#s created via the STRUCTURE or SCREEN commands must be searched in the structures files separately from text terms or profiles. The L# answer sets from structure searches can be used in crossover searches and can be combined with text terms.

=> s seidman e?/au,in;s theoret y?/au,in

'IN' IS NOT A VALID FIELD CODE
L40 112 FILE MEDLINE
L41 25 FILE HCAPLUS
L42 181 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L43 87 FILE EMBASE
L44 1 FILE WPIDS

TOTAL FOR ALL FILES
L45 406 SEIDMAN E?/AU,IN

'IN' IS NOT A VALID FIELD CODE
L46 20 FILE MEDLINE
L47 15 FILE HCAPLUS
L48 35 FILE BIOSIS
'IN' IS NOT A VALID FIELD CODE
L49 21 FILE EMBASE
L50 0 FILE WPIDS

TOTAL FOR ALL FILES
L51 91 THEORET Y?/AU,IN

=> s l45 and l51

L52 1 FILE MEDLINE
L53 1 FILE HCAPLUS
L54 6 FILE BIOSIS
L55 2 FILE EMBASE
L56 0 FILE WPIDS

TOTAL FOR ALL FILES
L57 10 L45 AND L51

=> dup rem l57

PROCESSING COMPLETED FOR L57
L58 7 DUP REM L57 (3 DUPLICATES REMOVED)

=> d tot all;fil medl,hcaplus,biosis,embase

L58 ANSWER 1 OF 7 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 1998253159 EMBASE
TI 6-Mercaptopurine metabolism in Crohn's disease [3] (multiple letters).
AU Ballinger A.; **Theoret Y.**; **Seidman E.G.**
CS A. Ballinger, Digestive Disease Research Centre, St Bartholomew's, Royal London Sch. of Med./Dentistry, 2 Turner Street, Whitechapel, London E1 2AT, United Kingdom
SO Gut, (1998) 43/2 (301).
ISSN: 0017-5749 CODEN: GUTTAK
CY United Kingdom
DT Journal; Letter
FS 005 General Pathology and Pathological Anatomy
037 Drug Literature Index
048 Gastroenterology
LA English
CT Medical Descriptors:
*crohn disease: DT, drug therapy
*crohn disease: ET, etiology
purine metabolism
drug metabolism
erythrocyte
disease activity
human
letter
priority journal
Drug Descriptors:
*mercaptopurine: DT, drug therapy
*mercaptopurine: PK, pharmacokinetics
*6 mercaptopurine derivative: PK, pharmacokinetics
RN (mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1

L58 ANSWER 2 OF 7 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1997:280731 BIOSIS
DN PREV199799579934
TI Intravenous 6-thioguanine (6-TG) prevents reactivation of trinitrobenzene sulfonic acid (TNBS)-induced colitis.
AU Cuffari, Carmen; **Theoret, Yves**; Latour, Sylvain; **Seidman, Ernest G.**
CS Dep. Pediatrics Pharmacol., Hopital Ste-Justine, Universite de Montreal, Montreal Canada
SO Gastroenterology, (1997) Vol. 112, No. 4 SUPPL., pp. A954.
Meeting Info.: Digestive Disease Week and the 97th Annual Meeting of the American Gastroenterological Association Washington, D.C., USA May 11-14, 1997
ISSN: 0016-5085.
DT Conference; Abstract
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Pathology, General and Miscellaneous - Therapy *12512
Digestive System - Pathology *14006
Pharmacology - Digestive System *22014
Routes of Immunization, Infection and Therapy *22100

Laboratory Animals - General *28002
BC Muridae *86375
IT Major Concepts
Digestive System (Ingestion and Assimilation); Methods and Techniques; Pathology; Pharmacology
IT Chemicals & Biochemicals
6-THIOGUANINE; TRINITROBENZENE SULFONIC ACID
IT Miscellaneous Descriptors
ANIMAL MODEL; DIGESTIVE SYSTEM; DIGESTIVE SYSTEM DISEASE; EFFECTS; GASTROINTESTINAL-DRUG; INTRAVENOUS ADMINISTRATION; PHARMACOLOGY; REACTIVATION PREVENTION; TRINITROBENZENE SULFONIC ACID-INDUCED COLITIS;
6-THIOGUANINE
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Sprague-Dawley rat (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman mammals; nonhuman vertebrates; rodents; vertebrates
RN 154-42-7 (6-THIOGUANINE)
2508-19-2 (TRINITROBENZENE SULFONIC ACID)

L58 ANSWER 3 OF 7 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:300477 BIOSIS
DN PREV199699022833
TI 6-Mercaptopurine (6-MP) metabolite levels in adult and pediatric IBD: Correlation with drug efficacy.
AU Cuffari, C. (1); **Theoret, Y.**; Lahaie, R.; **Seidman, E.**
CS (1) Div. Gastroenterol., Dep. Pediatrics, Univ. Montreal, Montreal, PQ Canada
SO Gastroenterology, (1996) Vol. 110, No. 4 SUPPL., pp. A890.
Meeting Info.: 96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week San Francisco, California, USA May 19-22, 1996
ISSN: 0016-5085.
DT Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Digestive System - Pathology *14006
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Digestive System *22014
Pediatrics *25000
BC Hominidae *86215
IT Major Concepts
Gastroenterology (Human Medicine, Medical Sciences); Metabolism; Pathology; Pediatrics (Human Medicine, Medical Sciences); Pharmacology
IT Chemicals & Biochemicals
6-MERCAPTOPURINE
IT Miscellaneous Descriptors
ANTIINFLAMMATORY-DRUG; CHILD; GASTROINTESTINAL-DRUG; INFLAMMATORY BOWEL
DISEASE; MEETING ABSTRACT; 6-MERCAPTOPURINE
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name

human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 50-44-2 (6-MERCAPTOPURINE)

L58 ANSWER 4 OF 7 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1996:300478 BIOSIS
DN PREV199699022834
TI Pharmacokinetics explain the lack of short-term efficacy of 6-mercaptopurine (6-MP) in the TNBS rat colitis model.
AU Cuffari, C. (1); **Theoret, Y.**; **Seidman, E.**
CS (1) Dep. Pediatric Gastroenterology, Hopital Ste-Justine, Univ. Montreal, Montreal, PQ Canada
SO Gastroenterology, (1996) Vol. 110, No. 4 SUPPL., pp. A890.
Meeting Info.: 96th Annual Meeting of the American Gastroenterological Association and the Digestive Disease Week San Francisco, California, USA May 19-22, 1996
ISSN: 0016-5085.
DT Conference
LA English
CC Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Pathology, General and Miscellaneous - Therapy *12512
Metabolism - Nucleic Acids, Purines and Pyrimidines *13014
Digestive System - Pathology *14006
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Digestive System *22014
BC Muridae *86375
IT Major Concepts
Digestive System (Ingestion and Assimilation); Metabolism; Pathology; Pharmacology
IT Chemicals & Biochemicals
6-MERCAPTOPURINE; 6-THIOGUANINE
IT Miscellaneous Descriptors
ANTIINFLAMMATORY-DRUG; BIOAVAILABILITY; GASTROINTESTINAL-DRUG; MEETING ABSTRACT; 6-MERCAPTOPURINE; 6-THIOGUANINE
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN 50-44-2 (6-MERCAPTOPURINE)
154-42-7 (6-THIOGUANINE)

L58 ANSWER 5 OF 7 MEDLINE DUPLICATE 1
AN 97038429 MEDLINE
DN 97038429
TI Quantitation of 6-thioguanine in peripheral blood leukocyte DNA in Crohn's
disease patients on maintenance 6-mercaptopurine therapy.
AU Cuffari C; **Seidman E G**; Latour S; **Theoret Y**
CS Department of Pediatrics, Hopital Sainte-Justine, Universite de Montreal, QC, Canada.
SO CANADIAN JOURNAL OF PHYSIOLOGY AND PHARMACOLOGY, (1996 May) 74 (5) 580-5.
Journal code: CJM. ISSN: 0008-4212.
CY Canada
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS Priority Journals
EM 199704
EW 19970401
AB The effects of 6-mercaptopurine (6MP) in inflammatory bowel disease are believed to be primarily mediated by its metabolite 6-thioguanine (6TG). Our aim was to develop an assay for measuring leukocyte DNA 6TG levels in patients with Crohn's disease, and to correlate them with levels of 6TG in erythrocytes. Heparinized blood was obtained from 15 adolescent Crohn's disease patients receiving 6MP at an average dose of 1.3 mg.kg-1 day-1 (range 0.8-1.6 mg.kg-1 day-1) for a mean of 23.7 months (range 3-71 months). Leukocyte DNA and erythrocyte 6TG levels were measured by an HPLC assay. Leukocyte 6TG levels ranged from 100 to 2305 pmol/mg DNA, while erythrocyte 6TG levels ranged from 64 to 1038 pmol/8 x 10(8) red blood cells, demonstrating significant interpatient variability. Leukocyte DNA 6TG levels correlated directly with erythrocyte 6TG levels, as measured by the Spearman rank correlation coefficient ($p < 0.05$). The HPLC measurement of erythrocyte and leukocyte DNA 6TG levels can be useful clinically in monitoring compliance, as well as perhaps to tailor drug metabolite levels to achieve the desired clinical effect.
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't
Adolescence
Adult
*Antimetabolites, Antineoplastic: BL, blood
Child
Chromatography, High Pressure Liquid: MT, methods
*Crohn Disease: BL, blood
Crohn Disease: DT, drug therapy
DNA: BL, blood
*DNA: CH, chemistry
Erythrocytes: CH, chemistry
*Immunosuppressive Agents: ME, metabolism
*Leukocytes: CH, chemistry
Leukocytes: ME, metabolism
Linear Models
Patient Compliance
*Thioguanine: BL, blood
*6-Mercaptopurine: ME, metabolism
RN 154-42-7 (Thioguanine); 50-44-2 (6-Mercaptopurine); 9007-49-2 (DNA)
CN 0 (Antimetabolites, Antineoplastic); 0 (Immunosuppressive Agents)

L58 ANSWER 6 OF 7 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1995:280768 BIOSIS
DN PREV199598295068
TI 6-Mercaptopurine (6-MP) metabolite measurement in IBD patients' neutrophils correlates with drug efficacy.
AU Cuffari, C. (1); **Seidman, E. (1); Theoret, Y.**
CS (1) Div. Gastroenterol., Dep. Pediatr., Cent. Recherche, Hop. Ste-Justine, Univ. Montreal, Montreal Canada
SO Gastroenterology, (1995) Vol. 108, No. 4 SUPPL., pp. A803.
Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association and Digestive Disease Week San Diego, California, USA May 14-17, 1995
ISSN: 0016-5085.
DT Conference
LA English

CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Cytology and Cytochemistry - Human *02508
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Pathology, General and Miscellaneous - Therapy *12512
Digestive System - Pathology *14006
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Blood, Blood-Forming Organs and Body Fluids - Blood, Lymphatic and Reticuloendothelial Pathologies *15006
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - Digestive System *22014
Pharmacology - Immunological Processes and Allergy *22018
Toxicology - Pharmacological Toxicology *22504
Pediatrics *25000
BC Hominidae *86215
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Gastroenterology (Human Medicine, Medical Sciences); Hematology (Human Medicine, Medical Sciences); Pathology; Pediatrics (Human Medicine, Medical Sciences); Pharmacology; Toxicology
IT Chemicals & Biochemicals
6-MERCAPTOPURINE; 6-THIOGUANINE
IT Miscellaneous Descriptors
ADOLESCENT; ERYTHROCYTE; GASTROINTESTINAL AGENT; IMMUNOSUPPRESSANT-DRUG; INFLAMMATORY BOWEL DISEASE; LEUKOCYTE; LEUKOPENIA; MEETING ABSTRACT; 6-MERCAPTOPURINE; 6-THIOGUANINE
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 50-44-2 (6-MERCAPTOPURINE)
154-42-7 (6-THIOGUANINE)

L58 ANSWER 7 OF 7 BIOSIS COPYRIGHT 1999 BIOSIS
AN 1994:287640 BIOSIS
DN PREV199497300640
TI Measurement of erythrocyte 6-mercapto-purine (6MP) metabolites in IBD patients: Correlation with efficacy and toxicity.
AU Cuffari, C.; **Theoret, Y.**; Duhaime, A.; **Seidman, E.**
CS Div. Gastroenterol., Dep. Pediatrics, Hopital Ste-Justine, Univ. Montreal,
Montreal Canada
SO Gastroenterology, (1994) Vol. 106, No. 4 SUPPL., pp. A1021.
Meeting Info.: 95th Annual Meeting of the American Gastroenterological Association New Orleans, Louisiana, USA May 15-18, 1994
ISSN: 0016-5085.
DT Conference
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Cytology and Cytochemistry - Human *02508
Biochemical Studies - General 10060
Pathology, General and Miscellaneous - Inflammation and Inflammatory Disease *12508
Pathology, General and Miscellaneous - Therapy *12512
Metabolism - General Metabolism; Metabolic Pathways *13002
Digestive System - Pathology *14006

Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Digestive System *22014
Pharmacology - Immunological Processes and Allergy *22018
Toxicology - Pharmacological Toxicology *22504
BC Hominidae *86215
IT Major Concepts
Blood and Lymphatics (Transport and Circulation); Cell Biology; Gastroenterology (Human Medicine, Medical Sciences); Metabolism; Pathology; Pharmacology; Toxicology
IT Chemicals & Biochemicals
6-MERCAPTO-PURINE; AZATHIOPRINE
IT Miscellaneous Descriptors
ANTIINFLAMMATORY-DRUG; AZATHIOPRINE; INFLAMMATORY BOWEL DISEASE; MEETING ABSTRACT; PHARMACOKINETICS; 6-MERCAPTOPURINE
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 50-44-2 (6-MERCAPTO-PURINE)
446-86-6 (AZATHIOPRINE)

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=> s (l5 or l6) and (gastrointest? or inflam? bowel? or ibd or crohn? or colitis)

L59 2 FILE MEDLINE
L60 2 FILE HCAPLUS
L61 0 FILE BIOSIS
L62 3 FILE EMBASE

TOTAL FOR ALL FILES
L63 7 (L5 OR L6) AND (GASTROINTEST? OR INFLAM? BOWEL? OR IBD OR CROHN?
OR COLITIS)

=> dup rem l63

PROCESSING COMPLETED FOR L63
L64 7 DUP REM L63 (0 DUPLICATES REMOVED)

=> d tot all

L64 ANSWER 1 OF 7 MEDLINE
AN 96086788 MEDLINE
DN 96086788
TI An intravenous loading dose of azathioprine decreases the time to response
in patients with **Crohn**'s disease.
AU Sandborn W J; Van O E C; Zins B J; Tremaine W J; Mays D C; Lipsky J J
CS Inflammatory Bowel Disease Clinic, Mayo Clinic, Rochester, Minnesota, USA.
NC FD-T-000-886 (FDA)
RR-00585 (NCRR)
SO GASTROENTEROLOGY, (1995 Dec) 109 (6) 1808-17.
Journal code: FH3. ISSN: 0016-5085.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals; Cancer Journals
EM 199603
AB BACKGROUND & AIMS: Azathioprine, an effective therapy for **Crohn**'s disease, is limited by a prolonged time to response. The aim of this study was to determine the safety and utility of a loading dose of azathioprine to decrease the time to response in patients with **Crohn**'s disease. METHODS: Twelve patients were studied: 6 with 13 fistulae and 6 with inflammatory disease. All patients received an intravenous infusion of azathioprine (50 mg/h for 36 hours). Response was determined by physical and radiographic examination for fistulae and by the **Crohn**'s Disease Activity Index for inflammatory disease. Erythrocyte concentrations of azathioprine metabolites were measured by chromatography. RESULTS: Seven of 13 fistulae closed by week 4, and three had a temporary decrease in drainage. One fistula improved at week 16. Two fistulae failed to improve. Four of 6 patients with inflammatory disease achieved remission, and 1 improved temporarily. Improvement was rapid (< or = 4 weeks). Peak concentrations of azathioprine metabolites occurred within 3 days. Clinical response did not correlate with azathioprine metabolite concentrations at the azathioprine dose studied. No adverse events occurred. CONCLUSIONS: An 1800-mg intravenous loading dose of azathioprine is safe and may decrease the time to response to < or = 4 weeks in patients with **Crohn**'s disease. Correlation between clinical response and azathioprine metabolite concentrations at larger azathioprine doses should be determined.
CT Check Tags: Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adult
Aged
*Azathioprine: AD, administration & dosage
Azathioprine: ME, metabolism
Azathioprine: TU, therapeutic use
Crohn Disease: BL, blood
***Crohn Disease: DT, drug therapy**
Erythrocytes: ME, metabolism
Guanine Nucleotides: BL, blood
*Immunosuppressive Agents: AD, administration & dosage

Immunosuppressive Agents: ME, metabolism
Immunosuppressive Agents: TU, therapeutic use
Infusions, Intravenous
Methyltransferases: BL, blood
Middle Age
Remission Induction
Thionucleotides: BL, blood
Time Factors
RN **15867-02-4 (6-thioguanylic acid)**; 446-86-6 (Azathioprine)
CN EC 2.1.1. (Methyltransferases); EC 2.1.1.67 (thiopurine methyltransferase); 0 (Guanine Nucleotides); 0 (Immunosuppressive Agents);
0 (Thionucleotides)

L64 ANSWER 2 OF 7 MEDLINE
AN 85254536 MEDLINE
DN 85254536
TI Phase II trials of hexamethylmelamine, dianhydrogalactitol, razoxane, and beta-2'-deoxythioguanosine as single agents against advanced measurable tumors of the pancreas. **Gastrointestinal** Tumor Study Group.
AU Anonymous
NC N01-CM-57032-57035 (NCI)
N01-CM-53844 (NCI)
N01-CM-67093-67097 (NCI)
SO CANCER TREATMENT REPORTS, (1985 Jun) 69 (6) 713-6.
Journal code: CNM. ISSN: 0361-5960.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals; Cancer Journals
EM 198511
AB Phase II trials of several single agents demonstrated only minimal objective response rates in patients with pancreatic carcinoma and measurable tumors: hexamethylmelamine (7%; four responses among 55 patients); dianhydrogalactitol (2.5%; one response among 40 patients); razoxane (7%; two responses among 29 patients); and beta-2'-deoxythioguanosine (6%; two responses among 32 patients). Among patients with a good performance status (0-2) and no prior chemotherapy, response rates were 8% for hexamethylmelamine (two responses among 26 patients); 8%
for dianhydrogalactitol (one response among 13 patients); 8% for razoxane (one response among 12 patients); and 10% for beta-2'-deoxythioguanosine (two responses among 20 patients). None of these agents given by the methods of this study offers substantive benefit to the patient with advanced pancreatic cancer.
CT Check Tags: Human; Support, U.S. Gov't, P.H.S.
*Adenocarcinoma: DT, drug therapy
*Altretamine: TU, therapeutic use
Antineoplastic Agents: TO, toxicity
*Antineoplastic Agents: TU, therapeutic use
*Deoxyguanosine: AA, analogs & derivatives
Deoxyguanosine: TU, therapeutic use
*Dianhydrogalactitol: TU, therapeutic use
Drug Evaluation
Leukopenia: CI, chemically induced
*Pancreatic Neoplasms: DT, drug therapy
*Piperazines: TU, therapeutic use
*Razoxane: TU, therapeutic use
*Sugar Alcohols: TU, therapeutic use
*Thionucleosides: TU, therapeutic use
Thrombocytopenia: CI, chemically induced

*Triazines: TU, therapeutic use
RN 21416-87-5 (Razoxane); 23261-20-3 (Dianhydrogalactitol); 645-05-6 (Altretamine); **789-61-7 (beta-2'-deoxythioguanosine)**; 961-07-9 (Deoxyguanosine)
CN 0 (Antineoplastic Agents); 0 (Piperazines); 0 (Sugar Alcohols); 0 (Thionucleosides); 0 (Triazines)

L64 ANSWER 3 OF 7 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 85181695 EMBASE
DN 1985181695
TI Phase II trials of hexamethylmelamine, dianhydrogalactitol, razoxane, and .beta.-2'-deoxythioguanosine as single agents against advanced measurable tumors of the pancreas.
SO Cancer Treatment Reports, (1985) 69/6 (713-716).
CODEN: CTRRDO
CY United States
DT Journal
FS 038 Adverse Reactions Titles
037 Drug Literature Index
016 Cancer
048 Gastroenterology
006 Internal Medicine
LA English
AB Phase II trials of several single agents demonstrated only minimal objective response rates in patients with pancreatic carcinoma and measurable tumors: hexamethylmelamine (7%; four responses among 55 patients); dianhydrogalactitol (2.5%; one response among 40 patients); razoxane (7%; two responses among 29 patients); and .beta.-2'-deoxythioguanosine (6%; two responses among 32 patients). Among patients with a good performance status (0-2) and no prior chemotherapy, response rates were 8% for hexamethylmelamine (two responses among 26 patients); 8%
for dianhydrogalactitol (one response among 13 patients); 8% for razoxane (one response among 12 patients); and 10% for .beta.-2'-deoxythioguanosine
(two responses among 20 patients). None of these agents given by the methods of this study offers substantive benefit to the patient with advanced pancreatic cancer.
CT Medical Descriptors:
*adverse drug reaction
*bone marrow depression
*cancer chemotherapy
*delusion
*drug comparison
*drug efficacy
*eye toxicity
gastrointestinal toxicity
*neurotoxicity
*pancreas carcinoma
*drug therapy
*phase 2 clinical trial
*vertigo
*visual impairment
*vomiting
pancreas
priority journal
blood and hemopoietic system
visual system
therapy
intoxication
nervous system

intravenous drug administration
human
clinical article
Drug Descriptors:
*altretamine
*deoxythioguanosine
*dianhydrogalactitol
*razoxane

RN (altretamine) 15468-34-5, 2975-00-0, 645-05-6; (deoxythioguanosine) **2133-81-5, 789-61-7**; (dianhydrogalactitol) 23261-20-3; (razoxane) 21416-67-1, 21416-87-5, 24584-09-6, 24613-06-7

L64 ANSWER 4 OF 7 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 85181690 EMBASE
DN 1985181690
TI Phase I evaluation of .beta.-2'-deoxythioguanosine in pediatric patients with leukemia.
AU Higgins G.R.; Jamin D.C.; Shore N.A.; et al.
CS Division of Hematology-Oncology, Childrens Hospital of Los Angeles, Los Angeles, CA 90054, United States
SO Cancer Treatment Reports, (1985) 69/6 (699-701).
CODEN: CTRRDO
CY United States
DT Journal
FS 038 Adverse Reactions Titles
037 Drug Literature Index
016 Cancer
025 Hematology
007 Pediatrics and Pediatric Surgery
030 Pharmacology
LA English
AB Thirty-one pediatric patients with acute leukemia who had relapsed on either 6-mercaptopurine or 6-thioguanine were treated with .beta.-2'-deoxythioguanosine, which was administered as an iv infusion every 12 hours for three or six doses every 2 weeks. Severe nausea and vomiting and urate nephropathy were the dose-limiting toxic effects. Therapeutic responses occurred in four of 24 children with acute lymphocytic leukemia and in two of seven with acute nonlymphoblastic leukemia.
CT Medical Descriptors:
*acute lymphocytic leukemia
*acute nonlymphocytic leukemia
*adverse drug reaction
*cancer combination chemotherapy
*cancer recurrence
*childhood cancer
*drug efficacy
***gastrointestinal toxicity**
*leukemia
*nausea
*nephrotoxicity
*drug therapy
*rash
*skin toxicity
*uric acid nephropathy
*vomiting
acute granulocytic leukemia
acute lymphoblastic leukemia
kidney disease
toxicity
kidney

intoxication
priority journal
therapy
blood and hemopoietic system
intravenous drug administration
human
child
clinical article
Drug Descriptors:
*deoxythioguanosine
*mercaptopurine
*tioguanine
allopurinol
RN (deoxythioguanosine) **2133-81-5, 789-61-7;**
(mercaptopurine) 31441-78-8, 50-44-2, 6112-76-1; (tioguanine) 154-42-7;
(allopurinol) 315-30-0
CO National cancer institute (United States)

L64 ANSWER 5 OF 7 EMBASE COPYRIGHT 1999 ELSEVIER SCI. B.V.
AN 83171004 EMBASE
DN 1983171004
TI Combination chemotherapy containing semustine (MeCCNU) in patients with advanced colorectal cancer previously treated with 5-fluorouracil (5-Fu).
AU Engstrom P.F.; MacIntyre J.M.; Muggia F.; et al.
CS Amer. Oncol. Hosp., Philadelphia, PA, United States
SO American Journal of Clinical Oncology: Cancer Clinical Trials, (1983) 6/2 (175-180).
CODEN: AJCODI
CY United States
DT Journal
FS 038 Adverse Reactions Titles
037 Drug Literature Index
016 Cancer
020 Gerontology and Geriatrics
LA English
AB Two hundred thirty-two patients with advanced measurable colorectal cancer previously treated with 5-fluorouracil (5-Fu) were randomized to one of the following treatments: A) semustine (MeCCNU) plus vincristine (VCR); B) MeCCNU plus dacarbazine (DTIC); C) MeCCNU plus DTIC plus VCR; D) MeCCNU plus beta-2'-deoxythioguanosine (.beta.-TGdR). Platelet nadirs <50,000/mm3 were noted in 9% (Treatment A) to 19% (D) of the patients while WBC nadirs <2,000/mm3 were noted in 7% (B) to 12% (C,D) of the patients. Severe vomiting was noted in 2% (D) to 14% (B) of the patients. The partial response rates and median survival times from date of randomization were as follows: Treatment A: 3/54 (6%), 19 weeks; B: 9/59 (16%), 28 weeks; C: 3/60 (5%), 25 weeks; D: 2/59 (4%), 19 weeks. Differences in response rate and median survival are not statistically significant.
CT Medical Descriptors:
*adverse drug reaction
*bone marrow depression
*cancer combination chemotherapy
*colon carcinoma
*drug comparison
gastrointestinal toxicity
*neurotoxicity
*drug therapy
*rectum carcinoma

*vomiting
cancer chemotherapy
intoxication
nervous system
blood and hemopoietic system
therapy
intravenous drug administration
human
large intestine
major clinical study
Drug Descriptors:
*dacarbazine
*deoxythioguanosine
*fluorouracil
*semustine
*vincristine
RN (dacarbazine) 4342-03-4; (deoxythioguanosine) **2133-81-5, 789-61-7**; (fluorouracil) 51-21-8; (semustine) 13909-09-6; (vincristine) 57-22-7

L64 ANSWER 6 OF 7 HCAPLUS COPYRIGHT 1999 ACS
AN 1973:413635 HCAPLUS
DN 79:13635
TI Preclinical toxicologic studies of .beta.-thioguanine deoxyriboside (NSC-71261)
AU Henry, M. C.; Morrison, R. K.; Brown, D. E.; Marlow, M.; Davis, R.; Cooney, D. A.
CS Res. Inst., Illinois Inst. Technol., Chicago, Ill., USA
SO Cancer Chemother. Rep., Part 3 (1973), 4(1), 41-9
CODEN: CCYPBY
DT Journal
LA English
CC 1-5 (Pharmacodynamics)
AB In dogs, .beta.-thioguanine deoxyriboside (I) [**789-61-7**] toxicity was characterized by the early development of pyrexia, leukopenia, anorexia, tonsillitis, pharyngitis, and marked thrombocytopenia; anemia developed later. In rhesus monkeys, anemia and leukopenia developed early while moderate reductions in the thrombocyte count occurred later. The leukopenia is essentially a granulocytopenia in both species. Hepatic and **gastrointestinal** toxic effects of I were evident in a few animals treated at high dose levels. The toxicity of I in mice and dogs was enhanced when I was administered in split doses rather than as a single injection.
ST Thioguanine deoxyriboside toxicity
IT **1688-22-8**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study)
(toxicity of)

L64 ANSWER 7 OF 7 HCAPLUS COPYRIGHT 1999 ACS
AN 1973:413459 HCAPLUS
DN 79:13459
TI Chronic toxicity of various classes of cancer chemotherapeutic agents
AU Henry, Mary C.
CS Res. Inst., Illinois Inst. Technol., Chicago, Ill., USA
SO U. S. Nat. Tech. Inform. Serv., PB Rep. (1972), No. 214546/4, 336 pp.
Avail.: NTIS
From: Govt. Rep. Announce. (U.S.) 1973, 73(7), 79
CODEN: XPBRCA
DT Report
LA English

CC 1-5 (Pharmacodynamics)
AB .alpha.-2'-Deoxythioguanosine (I) [**2133-81-5**] toxicity in dogs and monkeys is characterized by the early development of emesis, diarrhea, anorexia, and leukopenia, with later development of thrombocytopenia and neutropenia. The drug has low toxicity, and produced mortality in dogs only after daily administration of 4000 mg/m2 for 4 days. **Gastrointestinal** toxicity and significant thrombocytopenia were present only at high dose levels. A lethal dose was not found for monkeys on this dose regimen.
ST deoxythioguanosine toxicity leukopenia; thrombocytopenia neutropenia deoxythioguanosine toxicity
IT **2133-81-5**
RL: ADV (Adverse effect, including toxicity); BIOL (Biological study) (toxicity of)

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